UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/529,097	11/17/2005	Ernesto Arenas	0380-P02991US1	1994

25226 7590 12/09/2008
MORRISON & FOERSTER LLP
755 PAGE MILL RD
PALO ALTO, CA 94304-1018

EXAMINER	
HAMA, JOANNE	

ART UNIT	PAPER NUMBER
1632	

MAIL DATE	DELIVERY MODE
12/09/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/529,097	ARENAS ET AL.	
	Examiner	Art Unit	
	JOANNE HAMA	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 September 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5,14-16,18-24,26-29,31,32,40,46,47,52,54 and 56* is/are pending in the application.

4a) Of the above claim(s) *3,14,22-24,27,46,47,52,54 and 56* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4,5,15,16,18-21,26,28,29,31,32 and 40* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *6/1708;11/12/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant filed a response to the Non-Final Action of November 19, 2007 on May 19, 2008. An amendment to the claims was filed September 10, 2008, following a Notice of Non-Compliance, filed September 4, 2008. Claims 6-13, 17, 25, 30, 33-39, 41-45, 48-51, 53, 55, 57-67 are cancelled. Claims 1, 14-16, 18-20, 23, 26, 28, 40 are amended. Claims 3, 14, 22-24, 27, 46, 47, 52, 54, 56 are withdrawn.

Claims 1, 2, 4, 5, 15, 16, 18-21, 26, 28, 29, 31, 32, 40, drawn to an in vitro method of inducing promoting dopaminergic neuronal development. comprising expressing a transgene construct expressing a nucleic acid sequence encoding Nurr1 and treating the cells with Wnt-5a. The invention is also drawn to taking the neuronal cells from the claimed method and administering them to a patient.

This application contains claims 3, 14, 22-24, 27, 46, 47, 52, 54, 56 drawn to an invention nonelected with traverse in the reply filed on August 31, 2007. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

As a reminder, claim 5 is read as a nucleic acid construct comprising Nurr1, such that Nurr1 protein is introduced into a cell (see Restriction, June 1, 2007, page 4). "(P)reserving Nurr1 protein in the cell" is not part of the analysis.

Applicant indicates that claim 14 appears to have been inadvertently marked as withdrawn as it was not subject to restriction (Applicant's response, page 7). In response, claim 14 was withdrawn as the species election of claim 7 specifically indicated that one wnt be examined for analysis (Restriction, June 1,

2007, page 7). As Applicant has elected "wnt-5a" as the elected species (Applicant's response, August 31, 2007, page 11), the other species of wnt remain restricted until "wnt-5a" is allowed.

Information Disclosure Statement

Applicant filed Information Disclosure Statements (IDSes) June 17, 2008 and November 12, 2008. The IDSes have been considered.

Maintained Rejection

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 2, 4, 5, 15, 16, 18-21, 26, 28, 29, 31, 32, 40 remain rejected in modified form under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for

an in vitro method of inducing the expression of dopamine in a neural stem, progenitor, or precursor cell, or other stem cell, the method comprising expressing Nurr1 above basal levels within the cell and treating the cell with a Wnt-5a ligand, thereby inducing the expression of dopamine,

does not reasonably provide enablement for

an in vitro method of inducing or promoting dopaminergic neuronal development by enhancing proliferation, self-renewal, dopaminergic induction,

survival, differentiation and/or maturation in a neural stem, progenitor, or precursor cell, or other stem cell, the method comprising expressing Nurr1 above basal levels within the cell and treating the cell with a Wnt-5a ligand, thereby producing or enhancing proliferation, self-renewal, survival and/or dopaminergic induction, differentiation, survival , or acquisition of a neuronal dopaminergic phenotype,

wherein the dopaminergic cell is administered to an individual for treatment.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims, for reasons of record, November 19, 2007.

Applicant's arguments filed May 19, 2008 have been fully considered and they are persuasive in part.

Applicant indicates that claim 1 has been amended to methods of inducing or promoting dopaminergic neuronal development by enhancing proliferation, self-renewal, dopaminergic induction, survival, differentiation and/or maturation in a neural stem, progenitor or precursor cell, or other stem cell, comprising expressing a nuclear receptor of the Nurr1 subfamily above basal levels within the cell, and treating the cell with a Wnt-5a ligand, thereby producing or enhancing proliferation, self-renewal, survival, and/or dopaminergic inducing, differentiation, survival or acquisition of a neuronal dopaminergic phenotype (Applicant's response, page 9). Applicant indicates that with regard to the

Examiner relying on the citations of Sakurada et al., 1999 and Wagner et al., 1999 for teaching neurons at different stages of development have different requirements for developing into dopaminergic cells and with regard to Chung et al., 2002 for indicating that the expression of Nurr1 leads to TH expression by "seemingly different mechanisms," Applicant disagrees and indicates that the instant invention is based, in part, on the discovery that Nurr1 expression is an early step in dopaminergic neuron differentiation. Applicant refers to prior art teachings that a number of Nurr-1-derived dopaminergic neurons from a number of different sources, including ES cells, have been identified (Applicant's response, page 9). In response, this is persuasive and has indicated the enabled scope (see above), with regard using stem cells that overexpress Nurr1.

With regard to Applicant indicating that the Examiner indicates that the neither the specification nor the art provide guidance that introducing a Nurr1 expression construct and treatment with Wnt-5a are sufficient to induce a stem cell to develop into a dopaminergic neuron, Applicant disagree and refers to WO 00/66713 (Applicant's response, page 10). In response, as indicated above, with regard to the types of cells that can be used to overexpress Nurr1 and obtain dopaminergic cells, the Examiner has indicated as enabled, see above.

With regard to the Examiner indicating that the supernatants containing Wnt-5 can induce TH expression and that the teaching does not indicate that only Wnt-5a is required for TH expression, Applicant indicates the specification teaches that supernatants lacking Wnt-5a were used to illustrate that Wnt-5 specifically enhanced induction of TH expression in Nurr1 positive cells (parag.

184; note, this is parag. 173 in the PG publication US 2006/0233771) (Applicant's response, page 10). In response, this is persuasive and the rejection as it applies to this issue is withdrawn.

With regard to the issue of using other factors such as the activator of RXR, bFGF/FGF8/Shh, antioxidants or early glial cells without further guidance, Applicant indicates that parags. 73-80 of the specification provide guidance to test and evaluate what other factors may be used to enhance differentiation into dopaminergic neurons (Applicant's response, page 11). In response, this is persuasive, and the rejection as it applies to this issue is withdrawn.

With regard to the issue of using the instant cells in a method of transplantation, Applicant indicates that Wagner et al. teach on page 658, 2nd parag. on the left, indicates that a few c-42-derived dopaminergic cells displayed a high level of differentation and apparent integration into host tissue, showing that after dopaminergic induction, their phenotype is stable. Further, Applicant indicates that Parish et al., 2008, show that dopaminergic neurons induced from murine ventral mesencephalon cells by treatment with Wnt-5 were transplanted into brains for parkinsonian mice. A significant portion of implanted cells survived for 8 weeks and imparted functional correction of the parkinsonian defects (Applicant's response, page 11). In response, this is not persuasive. With regard to Wagner, et al., while Applicant indicates that Wagner et al. teach that few c-42 cells survived 12 days after transplantation in a mouse, this is not indicative that this is treatment of a parkinsonism patient. Further, Wagner et al. teach since few surviving TH-positive cells (that survived the transplant) could be detected,

exogenously applied trophic factors or supporting cells are required for long-term survival (Wagner et al., page 658, 1st col., 2nd parag.). With regard to Parish et al., Parish et al. teach that cells taken from the ventral midbrain (VM) and that they were transfected with expression constructs comprising the coding sequence of wnt-5a. Cells comprising the wnt-5a construct were cultured in the presence of FGF2/Shh/FGF8 before they were transplanted into parkinsonian nude mice (Parish et al., page 152, 1st col., 2nd parag. and page 157, Methods, under "VMN culture" and "6-OHDA lesioning and transplantation"). While Parish et al. teach that the grafts survived for 8 weeks and that the mice showed improvement in behavior (Parish et al., page 152, 2nd col.), Parish et al. do not provide guidance that any stem cell that overexpresses Nurr1 and is treated with wnt-5a is sufficient to treat Parkinson's disease following transplantation. First, as indicated above, Parish et al. teach that the wnt-5a treated cells were cultured in the presence of FGF2/Shh/FGF8. Parish et al. do not provide guidance that cells without this growth factor treatment can be used to treat Parkinson's disease. (It is noted that claim 31, which depends on claim 1, are drawn to cells without this treatment.) Given that neither the art nor the specification provides guidance for this to be the case, the claims are not enabled. Second, Parish et al. do not provide guidance that the instant invention can be practiced with any stem cell transfected with a Nurr1 expressing construct and that is Wnt-5 treated. As indicated in the previous Office Action, November 19, 2007, page 11, Sakurada et al., 1999, Development, 126: 4017-4026, abstract, teach that Nurr1 binding to the TH promoter in hippocampal precursors induces the expression of

TH, but does so in the absence of neuronal differentiation and without the expression of other dopaminergic cell markers. Given that Parish et al. teach that cells were taken from the ventral midbrain of E12.5-E12.7 rats (Parish et al., page 157, 2nd col., parag. 3) and that the cells were not transfected with a construct that expresses Nurr1, is indicative that Parish et al.'s cells used in the transplant have different characteristics from more primitive stem cells that are transfected with a Nurr1 construct. As such, an artisan cannot reasonably predict that stem cells transfected with a Nurr1 construct and treated with Wnt-5a necessarily are transplantable into Parkinson's patients. As such, the rejection as it applies to this issue remains.

With regard to the Examiner indicating that the specification does not provide guidance for transdifferentiating any neuron into a dopaminergic cell, Applicant has amended claims 1, 14, 15, 16, 20, 23, 26 (Applicant's response, page 11). In response, this is found persuasive and the rejection as it applies to this issue is withdrawn.

With regard to the predictability in differentiating cells from different species of animals that the instant invention can be practiced in, Applicant indicates that differentiation of dopaminergic neurons has been demonstrated by overexpression of Nurr1 in rat, mouse, and human cells (Applicant's response, page 12). In response, this is persuasive and the rejection as it applies to this issue is withdrawn.

Applicant indicates the Examiner indicates that the specification teaches that Wnt-5a was the only wnt protein that differentiated cells from rat E14.5

ventral mesencephala. Applicant indicates that the originally presented claims do not limit Wnt treatment to induction of differentiation. However, Applicant has amended the claims (Applicant's response, page 12). In response, Applicant's response is not persuasive. Applicant's amendment does not resolve the issue of enabled scope. Wnt-5a has the ability to induce dopamine expression, but does not have the ability to proliferate (see specification, page 2). As such, the full scope of biological activity that Wnt-5a has, per claim 1, is not enabled.

With regard to the specification not providing guidance to enable a method of treating an individual comprising administering a composition of dopaminergic cells made by the claimed method, Applicant disagrees. Applicant indicates that Wagner et al. describe c42-derived dopaminergic cells displayed apparent integration following implantation into the host. Applicant also refers to Parrish et al., 2008 (Applicant's response, page 13). In response, as discussed above, the teachings of Wagner et al. and Parish et al. are not indicative that the method of making dopaminergic cells from stem cells for transplantation into patients are enabled. While Parrish et al. teach a particular type of neural progenitor cells are treated with Wnt-5a and growth factors, this does not teach an artisan that more primitive cells such as ES cells that overexpress Nurr1 and are treated with Wnt-5a are able to integrate into a patient's brain following transplantation. As indicated by Sakurada et al., while cells can be made to express Nurr1 to induce the expression of tyrosine hydroxylase, this is not indicative that the cell also adopts characteristics of dopaminergic cells such that they can be transplanted.

Applicant indicates that the Examiner alleges that except for Parkinson's disease, nothing in the specification teaches a relationship between dopaminergic neurons and other neurodegenerative diseases (e.g. Alzheimer's disease). Applicant has amended the claims (Applicant's response, page 13). In response, this is persuasive and the rejection as it applies to this issue is withdrawn.

It is noted that the rejection of claim 7 is withdrawn as the claim is cancelled.

Conclusion

No claims allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joanne Hama, Ph.D. whose telephone number is 571-272-2911. The examiner can normally be reached Mondays, Tuesdays, Thursdays, and Fridays from 9:00-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras, can be reached on 571-272-4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history

information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public. For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

/Joanne Hama/
Primary Examiner
Art Unit 1632